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10/031,158	01/11/2002	Ira Pastan	4239-61854	8170

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,158	PASTAN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,10,15-17,20 and 24-58* is/are pending in the application.

4a) Of the above claim(s) *29-33,36-44 and 48-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,10,15-17,20,24-28,34,35,45-47 and 56-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20041111*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed November 11, 2004 is acknowledged and has been entered. Claims 5, 18, and 19 have been canceled. Claims 1-4, 6, 16, 17, 27-29, 34, and 50 have been amended. Claims 55-58 have been added.

2. The declaration under 37 C.F.R. § 1.132 by Dr. Ira Pastan and Dr. Jay A. Berzofsky filed November 11, 2004, is acknowledged and has been entered.

3. Claims 1-4, 6, 10, 15-17, 20, and 24-58 are pending. Claims 29-33, 36-44, and 48-55 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed November 11, 2004.

4. Claims 1-4, 6, 10, 15-17, 20, 24-28, 34, 35, 45-47, and 56-58 are currently under prosecution.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Election/Restrictions

7. At page 14 of the amendment filed November 11, 2004, Applicant has affirmed the election with traverse to prosecute the invention of group I, claims 1-6, 10, 15-20, 24-28, 34, 35, and 45-47, as set forth in the restriction and election requirement.

Applicant' argument at page 14 of the amendment traversing the restriction and election requirement is acknowledged. Applicant has argued that the restriction and election requirement

is improper because it would not be a serious burden to search the invention of Group V together with the invention of Group I.

Applicant's argument has been carefully considered but not found persuasive for the following reason:

The invention of Group I is a polypeptide, a nucleic acid molecule encoding said polypeptide, a vector comprising said nucleic acid molecule, and a method for eliciting an immune response in a subject comprising administering to the subject a composition comprising said polypeptide. In contrast, the invention of Group V is an antibody.

Applicant has argued that it would not constitute a serious burden to search both inventions; however, the burden of search is a criterion not considered in National Stage applications filed under 35 U.S.C. § 371.

As stated in the previous Office action, the special technical feature of the invention of Group I is making and using a polypeptide; in contrast, the special technical feature of the invention of Group V is making an antibody.

The restriction and election requirement is proper because the inventions of Groups I and V do not share the same or corresponding special technical feature, so as to form a single general inventive concept under PCT Rules 13.1 and 13.2, since PCT Rules 13.1 and 13.2 do not provide for a single general inventive concept to comprise more than the first mentioned product, the first mentioned method for making said product, and the first mentioned method for using said product.

Accordingly, the restriction and election requirement is deemed proper and therefore made FINAL.

8. Newly submitted claim 55 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The inventions of Group I are polypeptides comprising the amino acid sequence of SEQ ID NO: 14 or immunogenic fragments thereof, nucleic acid molecules encoding said polypeptides, vectors comprising said nucleic acid molecules, and method for eliciting an immune response in a subject comprising administering to the subject a composition comprising

said polypeptides. In contrast, the inventions of claim 55 are polypeptides that comprise amino acids 42 to 57 of SEQ ID NO: 15.

The specification discloses that the polypeptide of SEQ ID NO: 15 is structurally distinct from the polypeptide of SEQ ID NO: 14; see, e.g., page 7, lines 6-15. Accordingly, the elected invention of Group I and the invention of claim 55 are patentably distinct.

Because the products of the elected group of claims and the products of claim 55 are different proteins comprising distinct amino acid sequences, the necessary searches are not the same, nor are they coextensive in nature and scope with one another. A search of relevant sequence databases using the entire amino acid sequence of the polypeptide as query is necessary for the determination of the novelty and unobviousness of either of the different polypeptides; as these sequences are different, so are the searches. Furthermore, a thorough search of the technical literature is particularly pertinent in this art. For each different invention, the search of appropriate databases would be performed using a different set or series of key words; therefore, the searches of the technical literature are also different. Consequently, having to search both the inventions of Group I and the inventions of claim 55 would constitute a serious burden.

Since the inventions of Groups I and the inventions of claim 55 are patentably distinct and because the examination of both could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 55 has been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

9. Applicant's remarks addressing the priority claim at pages 14-18 of the amendment filed November 11, 2004, are acknowledged and have been considered.

Applicant's amendment to the claims has perfected Applicant's claim under 35 USC § 120 for benefit of the earlier filing date of the PCT/US00/19039, filed July 12, 2000, which claims benefit of US Provisional Application No. 60/157,471, filed October 1, 1999.

However, the present claims are not entitled to the claimed benefit of the earlier filing dates of US Provisional Application No. 60/143,560, filed July 13, 1999, for the following reasons:

US Provisional Application No. 60/143,560 provides an insufficient disclosure of the claimed invention to meet the enablement and written description requirements set forth under 35 USC § 112, first paragraph. In particular, US Provisional Application No. 60/143,560 does not provide an adequate description of the amino acid sequence set forth as SEQ ID NO: 14, or of the polynucleotide sequence set forth as SEQ ID NO: 13 to enable one skilled in the art to make and use the claimed invention. Therefore, the earliest effective filing date of the instant claims is the filing date of US Provisional Application No. 60/157,471, filed October 1, 1999.

Information Disclosure Statement

10. The information disclosure filed November 11, 2004, has been considered. An initialed copy is enclosed.

Oath/Declaration

11. Receipt of the new declaration filed November 11, 2004 in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date acknowledged.

Grounds of Objection and Rejection Withdrawn

12. Unless specifically reiterated below, the amendment filed November 11, 2004, has obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed August 5, 2004.

Response to Amendment

13. The amendment filed on November 11, 2004, is considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution, rather than mailing a Notice of Non-Compliant Amendment, Applicant is advised to correct the following deficiency in replying to this Office action:

The amendment is non-compliant because the status identifiers in parentheses of claims that have been withdrawn from further consideration do not properly indicate that status.

Briefly, the revised amendment practice now requires a listing of all claims beginning on a separate sheet. Each claim ever presented must be included in the listing of claims together with a single proper status identifier in parentheses. The permissible status identifiers include: "original", "currently amended", "canceled", "withdrawn", "previously presented", "new", and "not entered". The text of all pending claims, including withdrawn claims, must be presented. Markings to show only the changes made in the current amendment relative to the immediate prior version should be included with the text of all currently amended claims, including withdrawn claims that are amended. Added text must be shown by underlining the added text. Generally deleted text must be shown by strikethrough (e.g., ~~strikethrough~~); or if the strikethrough cannot be easily perceived, and for deletion of five or fewer characters, the deleted text may be marked by the inclusion of deleted text in double brackets (e.g., [[444]]). The text of "canceled" and "not entered" claims must not be presented; and consecutive "canceled" or "not entered" claims may be grouped together in one line (e.g., Claims 1-11 (canceled); Claims 51-62 (not entered)).

For further explanation of the amendment format required by 37 CFR § 1.121, see MPEP § 714 and the USPTO website at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf.

14. The declaration under 37 C.F.R. § 1.132 by Dr. Ira Pastan and Dr. Jay A. Berzofsky filed November 11, 2004, is sufficient to overcome the rejection of claims 2, 16, 45, and 46 based upon the insufficiency of the disclosure to enable the skilled artisan to make and use the claimed invention for the reasons set forth in section 21 of the previous Office action.

Although the skilled artisan cannot use the claimed invention to treat prostate cancer and TARP-expressing breast cancer without undue experimentation, at the very least, it is believed that the declaration shows that the invention can be used to enumerate peptide-specific CD8+ cells in prostate patients, which data could potentially be used, for example, to select candidate

peptides, since for the most part, only patients having peptide-reactive cytotoxic T lymphocytes (CTL) will mount an effective immune response after immunization with that peptide, and also to select appropriate patients for participation in clinical trials to determine if immunizing patients with TARP, or an immunogenic fragment thereof, can provide clinically significant therapeutic benefit.

Grounds of Objection and Rejection Maintained

Specification

15. The objection to the disclosure because of sequences appearing in the specification and/or drawings, which are not properly identified by sequence identifier in accordance with 37 C.F.R. 1.821(d), is maintained.

It was noted in section 15 of the previous Office action that sequences are depicted in Figure 14, which are not properly identified by sequence identification numbers.

It appears that Applicant has made a *bona fide* attempt to resolve this issue by amending the Brief Description of the Drawings at page 10 of the specification. However, it appears that Figure 14A depicts a *continuous* amino acid sequence of "TARP", which is not identified.

Again, sequence identifiers for sequences appearing in the drawings may appear in the Brief Description of the Drawings. Appropriate action correcting this deficiency is required.

Claim Rejections - 35 USC § 112

16. The rejection of claim 26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

This is a new matter rejection; the ground of rejection is set forth in section 20 of the previous Office action.

At page 19 of the amendment filed November 11, 2004, Applicant has traversed this ground of rejection, arguing written support for the recitation of the limitation in claim 26, "wherein said subject is a female at risk for developing breast cancer", is found at page 28, lines

19-21, and page 23, lines 11-14. Applicant has asserted that if one inserts the definition of prophylactic found in the specification at page 23 into the disclosure at page 28, one would arrive at the conclusion that "TARP polypeptides can be administered to woman [sic] who does not exhibit signs of breast cancer or exhibits only early signs of breast cancer for the purpose of decreasing the risk of developing breast cancer, to provide an immune defense in the event that a TARP-expressing breast cancer develops" (page 19, paragraph 4).

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As previously stated, the disclosure at page 28 (lines 19-21) to which Applicant has referred provides a description of administering a composition to "women prophylactically to provide an immune defense in the event that a TARP-expressing breast cancer develops later". This disclosure, however, does not suggest administering to women at any particular risk; nor does it *adequately describe* a subpopulation of females at particular risk for developing breast cancer.

Contrary to Applicant's assertion, the definition of "prophylactically" is not at question, since the term "prophylactic" is ordinarily understood to mean "preventive". Notably, if a subject is at "risk" for developing a certain disease (e.g., cancer), prophylactic therapy may tend to prevent or ward off disease, but does not alter the intrinsic tendency of the patient to develop the disease due to the presence of, or exposure by one or more "risk factors" (e.g., asbestos exposure; genetic predisposition; a long history of cigarette smoking).

The issue, however, is that the disclosure does not appear to provide written support for the particular breadth and scope of the claim. The disclosure provides written support for administering the composition to a woman in the event that a TARP-expressing breast cancer develops in the woman, but the disclosure does not describe a woman at any particular risk for developing breast cancer, such as a woman that is genetically predisposed by heritable mutations in, for example, the tumor suppressor BRCA1. Moreover, the description of a female in which a TARP-expressing breast cancer may later develop does not suffice to describe a female at risk for developing, in particular, breast cancer.

Accordingly, contrary to Applicant's assertion, the specification, including the claims, as originally filed, does not appear to provide proper and sufficient written support for recitation of the limitation in claim 26.

This issue may be remedied by amending claim 26 to recite, for example, "wherein the composition is administered to a female subject to provide an immune defense in the event that a TARP-expressing breast cancer later develops in the female".

17. The rejection of claims 1, 3, 4, 6, 10, 15, 17, 20, 24-28, 34, 35, 47, 56, and 57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

This is a written description rejection; the ground of rejection is set forth in section 21 of the previous Office action.

At pages 20-24 of the amendment filed November 11, 2004, Applicant has traversed this ground of rejection, arguing that the amended claims are directed to a genus of polypeptides comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 that are expressed in prostate cancer cells, breast cancer cells, or both types of cells. Because computer programs are available that can be used to determine the percent identity of any given amino acid sequence, relative to SEQ ID NO: 14, Applicant has submitted the skilled artisan could immediately recognize or distinguish the members of the claimed genus of polypeptides. Furthermore, Applicant has submitted that, since the claimed polypeptides comprise an amino acid sequence that is at least 90% identical to SEQ ID NO: 14, in a polypeptide consisting of the amino acid sequence of SEQ ID NO: 14, at most only five amino acids can be substituted by others, and since the specification discloses that the polypeptide comprises a putative leucine zipper domain, a cAMP phosphorylation site, a GMP phosphorylation site, the claimed polypeptides can be immediately recognized or distinguished by determining the presence of these structural features. Regarding claims directed to polypeptides comprising an epitope of a protein having the amino acid sequence of SEQ ID NO: 14, Applicant has asserted that the written description of the claimed invention is adequate, since

the disclosure teaches that epitopes are composed of 8-10 amino acids and have anchoring residues and describes methods by which the immunogenicity of peptides can be characterized. Moreover, Applicant has asserted that, because MHC binding motifs were known in the art, the structures of epitopes can be predicted using computer algorithms, such as those disclosed by Sturniolo et al., Manici et al., and Brusic et al. (Exhibits A-C, respectively).

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

See MPEP § 2163.

That the written description requirement set forth under 35 USC § 112, first paragraph, is met, the supporting disclosure must reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. That the disclosure reasonably convey that Applicant had possession of the claimed invention, the written description of the claimed invention must be sufficient to allow the skilled artisan to immediately envision, recognize, or distinguish claimed invention.

In reply to Applicant's arguments, although claims 4 and 56-58 are drawn to polypeptides that comprise an amino acid sequence that is at least 90% identical to SEQ ID NO: 14, nucleic acid molecules encoding such polypeptides, or methods for using such polypeptides, because the polypeptides do not necessarily have any particularly identifying functional feature that correlates with the presence of this recited structure feature, the claims are directed to a genus of polypeptides, which although marginally related in structure, can vary substantially in function. Claims 1, 3, 6, 10, 15, 17, 20, 24-28, 34, 35, 47 are directed to an even broader genus of polypeptides that comprise an immunogenic epitope of eight to ten amino acids of a polypeptide comprising SEQ ID NO: 14, or at least 10 consecutive amino acids of SEQ ID NO: 14; and claims 27, 34, and 35 are further directed to another genus of polypeptides comprising an epitope of the protein having the amino acid sequence of SEQ ID NO: 14. Because these polypeptides

merely comprise at least 8 amino acids of the amino acid sequence of SEQ ID NO: 14 or of a polypeptide comprising SEQ ID NO: 14, and apparently have no particular common function, the claims are directed to genera of polypeptides varying even more markedly in structure and function than the genus of polypeptides to which claims 4 and 56-58 are directed.

Although Applicant has submitted that the amino acid sequence of the TARP (i.e., SEQ ID NO: 14) contains putative functional domains, such as a leucine zipper, the function of the polypeptide of SEQ ID NO: 14 is not described. Moreover, although the polypeptide of SEQ ID NO: 14 may indeed be found to have a functional leucine zipper domain, the protein or proteins to which the polypeptide of SEQ ID NO: 14 interact through this domain have not been described. Accordingly, the description of the polypeptide of SEQ ID NO: 14 cannot be considered representative of at least a substantial number of members of the claimed genus of polypeptides, because, although the members of the genus have varying functions, the specification has not described the functional and structural attributes of the polypeptide of SEQ ID NO: 14 that are characteristic of at least most of the claimed genus of polypeptides. "[W]here there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure 'indicates that the patentee has invented species sufficient to constitute the gen[us].' See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615". MPEP § 2163.

Applicant has submitted that because the polypeptides are expressed in breast or prostate cancer cells, the polypeptide can be recognized or distinguished; however, were the skilled artisan given two polypeptides comprising an amino acid sequence at least 90% identical to SEQ ID NO: 14, one of which is expressed in prostate or breast cancer cells and the other not, the skilled artisan could not immediately recognize or distinguish the polypeptide expressed in prostate or breast cancer cells, since the polypeptide has not been described as having any particularly identifying functional feature attributable to the presence of an amino acid sequence that is at least 90% identical to SEQ ID NO: 14. In addition, the claims are not necessarily drawn to a polypeptide expressed naturally by prostate and/or breast cancer cells; and virtually any polypeptide can be expressed recombinantly in either of type of cells.

Applicant has submitted that in a protein the size of TARP (i.e., 58 amino acids), at most only 5 amino acids can be substituted by other amino acids in any of the members of the claimed genus of claimed polypeptides, but the specification has not described the amino acids that are critical to the function of the protein, nor has the specification described by which other amino acids the critical amino acids can be replaced, such that the variant retains that function. Still, since the function of TARP is not described, one could not recognize such a protein by its function and therefore one could not immediately distinguish members of the claimed genus of polypeptides that retain that function. Even if the skilled artisan were able to submit a complete list of polypeptides comprising an amino acid sequence that is at least 90% identical to SEQ ID NO: 14, the skilled artisan could not recognize which of these would function similarly to a protein comprising SEQ ID NO: 14, and which would not.

Applicant has remarked that the specification shows a portion of the amino acid sequence of SEQ ID NO: 14 is homologous to portions of proteins occurring in yeast cells and cellular slime moulds. However, since the function of the protein of SEQ ID NO: 14 is not described, there is no apparent correlation between any of the conserved amino acids, domains, or motifs and any particular function. Even so, as evidenced by Skolnick et al. (of record) and Bowie et al. (of record), the arts of biochemistry and molecular biology are unpredictable. Despite observed homologies in the amino acid sequences of different proteins, the conservation of certain amino acids cannot be relied upon to assign functions to homologues of proteins having known functions. Moreover, as Applicant has noted, Skolnick et al. teaches proteins are multifunctional; because proteins are multifunctional, it cannot be predicted which conserved amino acids are essential to which functions, since some these residues are essential to one function but not another.

Applicant has remarked that it is not clear why Skolnick et al. and Bowie et al. suggest that the written description is too inadequate to meet the requirement set forth under 35 USC § 112, first paragraph. Again, Skolnick et al. and Bowie et al. provide evidence that the art is unpredictable. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (*supra*) state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows

that in this instance, an adequate written description of the claimed genus of polypeptides cannot be achieved by the description of the polypeptide of SEQ ID NO: 14, particularly since the polypeptide of SEQ ID NO: 14 is not evidently representative of the genus as a whole.

Applicant has asserted that having described epitopes as consisting of 8-10 amino acids and having anchoring residues, the written description requirement is met. Furthermore, Applicant has asserted that computer algorithms can predict the structures of peptide epitopes, which are fragments of a polypeptide comprising SEQ ID NO: 14, that bind MHC class I and class II molecules; however, as evidenced by Lu et al., Zaks et al., and Lee et al. (all of record), one still cannot reliably and accurately predict the structures of immunogenic fragments that can be used to stimulate an effective antitumor immune response. Again, Applicant is reminded that the written description provision of 35 U.S.C. § 112, first paragraph, is severable from its enablement provision; so adequate written description requires more than mere references to *potential* methods for predicting the structures of suitable epitopes. An adequate written description of a chemical invention requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3D 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In this instance, despite knowledge of potential methods for identifying candidate peptides, the written description requirement has not been met since the skilled artisan cannot immediately envision, recognize, or distinguish the genus of polypeptides comprising an epitope of the protein having the amino acid sequence of SEQ ID NO: 14. As defined by Greenspan, the disclosure does not include an adequate description of an "epitope", since the molecular interface between the amino acid residues of the disclosed immunogenic peptides and the amino acids of the MHC molecule to which the peptides bind has not been described; rather, what has been described are immunogenic peptides that bind MHC class I molecules. However, the disclosure does not include an adequate description of at least a substantial number of the peptide fragments of the polypeptide of SEQ ID NO: 14 that bind MHC class I molecules expressed by CD8+ T cells; and because these peptides vary substantially in structure, as each comprises a different amino acid sequence, those immunogenic peptide fragments of the polypeptide of SEQ ID NO: 14 that are described are not representative of the genus as a whole. Additionally, since the claimed polypeptides merely comprise an

epitope of the polypeptide of SEQ ID NO: 14 (i.e., 8-10 amino acids), the polypeptides vary substantially in structure and function. With particular regard to claims 27, 34, and 35, realize that claims are further directed to a genus of polypeptides comprising an epitope of a protein *comprising* SEQ ID NO: 14; the epitope is not necessarily derived from the amino acid sequence of SEQ ID NO: 14 (it could be derived from the portion of the protein having the amino acid sequence of SEQ ID NO: 14, which has not been described). Accordingly, the antigen presenting cells of claims 27, 34, and 35 may stimulate an immune response against another antigen, not necessarily against the polypeptide of SEQ ID NO: 14. Consequently, in the absence of a detailed description of at least a substantial number, or a representative number of the members of the polypeptides to which the claims are directed, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Similarly, claim 3 is drawn to a genus of polypeptides that differ markedly in both structure and function, since the claim merely requires the claimed polypeptides to comprise at least ten consecutive amino acid residues of SEQ ID NO: 14. As explained above, the polypeptide of SEQ ID NO: 14 is not representative of the claimed genus of polypeptides; moreover, because there is no correlation between the recited structure feature that is common to the genus of polypeptides (i.e., an amino acid sequence comprising at least 10 consecutive amino acids of SEQ ID NO: 14) and any particularly identifying functional feature that is shared by at least a substantial number of its members, the skilled artisan could not immediately envision, recognize, or distinguish the claimed polypeptides from others.

Accordingly, although carefully considered, Applicant's arguments have not been found persuasive.

These issues may be remedied by amending claims 1 and 4, so that the claims are limited to a polypeptide comprising SEQ ID NO: 14; amending claim 3, so the claim is limited to a polypeptide consisting of at least 10 consecutive amino acids of the amino acid sequence of SEQ ID NO: 14; amending claim 17, so the claim is limited to a nucleic acid molecule encoding a polypeptide consisting of an immunogenic fragment of eight to ten consecutive amino acids of the amino acid sequence of SEQ ID NO: 14; and amending claim 27, so that the claim is limited

to antigen-presenting cells pulsed with a peptide consisting of a fragment of the amino acid sequence of SEQ ID NO: 14.

18. The rejection of claims 1, 3, 4, 6, 10, 15, 17, 20, 24-28, 34, 35, 47, and 56-58 35 U.S.C. 112, first paragraph, is maintained because the specification, **while being enabling for making and using** a polypeptide, or composition thereof, comprising the amino acid sequence of SEQ ID NO: 14 and a nucleic acid molecule encoding the aforementioned polypeptide, **does not reasonably provide enablement for making and using** a polypeptide comprising an immunogenic polypeptide comprising an immunogenic epitope of 8-10 consecutive amino acids of the amino acid sequence of SEQ ID NO: 14, a polypeptide comprising at least 10 consecutive amino acids of SEQ ID NO: 14, a polypeptide comprising an amino acid sequence with at least 90% identity to the amino acid sequence of SEQ ID NO: 14, a nucleic acid molecule encoding any of the aforementioned polypeptides, a vector comprising said nucleic acid molecule, a nucleic acid molecule encoding a polypeptide comprising an immunogenic epitope of 8-10 consecutive amino acids of SEQ ID NO: 14, a method for eliciting an immune response in a subject comprising administering to a subject a composition comprising any of the aforementioned polypeptides, . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This is a scope of enablement rejection; this ground of rejection is set forth in section 22 of the previous Office action.

At pages 24-29 of the amendment filed November 11, 2004, Applicant has traversed this ground of rejection, arguing, in particular, that the declaratory evidence under 37 C.F.R. § 1.132 shows that the skilled artisan could make and use the claimed invention without the need to first perform additional, undue experimentation.

Applicant's arguments and particularly the merit of the declaration under 37 C.F.R. § 1.132 by Dr. Ira Pastan and Dr. Jay A. Berzofsky have been carefully considered but not found persuasive for the following reasons:

Again, inquiry as to whether undue experimentation is required to make and use the claimed invention involves a consideration of factors described by *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Applicant has argued that the structure of peptides suitable for use in stimulating an antitumor immune response can be predicted using computer algorithms; however, at pages 2 and 3, the declaration by Dr. Ira Pastan and Dr. Jay A. Berzofsky states that to the contrary, these computer algorithms cannot be used to reliably and accurately select fragments of the amino acid sequence of SEQ ID NO: 14 to make peptides that are capable of binding specifically to MHC class I molecules. The declaration states that only two of four "TARP peptides", each of which was predicted using a computer program to comprise an HLA-A2.1 binding epitope, "showed measurable binding capacity to HLA-A2.1 molecules" (page 3, paragraph 1).

Thus, the declaratory evidence supports the position that the claimed invention cannot be made and used without the need to first perform additional, undue experimentation. As suggested by the references cited in the previous Office action (e.g., Lu et al.), the structure of immunogenic peptides that are capable of binding MHC molecules and eliciting an effective antitumor immune response cannot be predicted but can only be determined empirically.

The declaration shows that the TARP peptides selected for their ability to bind HLA-A2.1 are immunogenic in transgenic mice expressing HLA-A2.1, i.e., capable of stimulating CD8+ cells expressing HLA-A2.1. After restimulation *in vitro*, these CD8+ cells are capable of lysing peptide-pulsed Jurkat cells transfected with HLA-A2, and upon restimulation, capable of producing IFN-γ (pages 3 and 4). Furthermore, the declaration shows that a HLA-2.1+ patient having prostate cancer has CD8+ cells that are stimulated in the presence of both peptides determined to bind HLA-A2.1; and these CD8+ cells are capable of lysing peptide-pulsed target cells, which express HLA-A2.1 (pages 4 and 5). The declaration also shows that these CD8+ cells are capable of lysing breast (MCF7) and prostate (LNCaP) cancer cells that express both HLA-A2.1 and TARP (i.e., the polypeptide of SEQ ID NO: 14); however, the declaration states that the CD8+ cells showed only marginal cytolytic activity against LNCaP cells (page 5). Finally, the declaration shows that the frequency of peptide-specific CD8+ cells in prostate cancer patients can be assessed using the "tetramer assay".

Upon the basis of this declaratory evidence, Applicant has argued that the claimed invention is enabled by the supporting disclosure and can be used by the skilled artisan without need to first perform additional, undue experimentation. In reply, although impressive, the declaratory evidence is not reasonably commensurate in scope with the breadth of the claims. Moreover, the declaration provides evidence that the skilled artisan cannot predict which peptide fragments are capable of binding MHC class I molecules. Furthermore, despite the declaratory evidence, the preponderance of factual evidence of record supports the position that the instant disclosure is not sufficient to satisfy the enablement provision of 35 U.S.C. § 112, first paragraph. For example, Lee et al. and Gao et al. (both or record) teach that despite peptide-induced T cell reactivity, the tumors failed to regress; accordingly, it has been suggested in the previous Office action that the endpoints measured by the studies described in Applicant's declaration do not accurately predict or estimate the effectiveness of immunizing a patient having cancer with the claimed invention.

In the IDS filed together with the recent amendment, Applicant has newly cited Oh et al. (*Cancer Research.* 2004 Apr 1; **64**: 2610-2618). This reference reports the data that is set forth by Applicant's declaration under 37 C.F.R. § 1.132. Notably, Oh et al. teaches that in efforts to enhance the binding affinity of the natural TARP peptides to HLA-A2.1 molecules, substitutions of the amino acids at positions 2, 3, and 9, the "anchoring residues" to which Applicant has referred in their rebuttal, were made (page 2612, column 2). Oh et al. found that the effects of such substitutions cannot be accurately predicted, since replacement of these amino acids by others, which are more highly conserved at those sites within the HLA-A2.1 binding motif, in different peptides produced different effects; some substitutions increased the binding affinity, others did not influence the binding affinity or precluded binding. Thus, the results reported by Oh et al. lend further support to the position that the art too highly unpredictable to enable the skilled artisan make and use the claimed invention without undue experimentation.

In addition, Oh et al. teaches that $TARP_{27-35}$ induces CD8+ cells, but these cells are not reactive against the other peptide, $TARP_{29-37}$, or its affinity-enhanced variants (page 2613, column 1). Peptide-specific CD8+ cells are not necessarily cross-reactive. These results emphasize the need to first determine if a patient has peptide-reactive CD8+ cells, or if a peptide is capable of stimulating CD8+ cells in the patient before attempting to use the claimed invention

to stimulate an immune response in the patient. Furthermore, Oh et al. teaches that CD8+ cells stimulated by $TARP_{27-35}$ were more cytolytic than cells stimulated by $TARP_{29-37}$ (page 2613, column 2); and although the affinity-enhanced $TARP_{29-37-3A}$ peptide variant has a higher MHC-binding affinity than $TARP_{29-37-9V}$, only the latter stimulated CD8+ cells that recognize the MHC complex with the naturally processed peptide (page 2613, column 2, through page 2614, column 2). As may be expected, because the $TARP_{29-37-3A}$-stimulated CD8+ cells did not efficiently recognize the naturally processed peptide, these CD8+ cells were less capable of lysing MCF7 breast cancer cells than the CD8+ cells stimulated by the other peptides (page 2615, Figure 7).

Together, the results of Oh et al. underscore the state of the art and provide further evidence that the skilled artisan cannot yet predict which peptide fragments of a given tumor antigen, such as TARP, are capable of use in stimulating an effective immune response against tumor cells that express the antigen. Therefore, Oh et al. provides further evidence that the amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to make and use the claimed invention without first having to perform additional empiric studies of an undue, rather than routine, nature.

At pages 25-28, Applicant has addressed the teachings of Wolfgang et al., cited in support of the Office's position that the supporting disclosure does not reasonably enable the skilled artisan to make and use the claimed invention. Applicant's remarks have been considered, but it cannot be disputed that Wolfgang et al. teaches "it is not yet possible to establish the role of TARP in prostate cancer cell growth or normal growth" (page 8126, column 1). Although, as Applicant has noted, Wolfgang et al. further discloses that their results support the proposition that the expression of TARP is involved a pathway that modulates oncogenesis, Wolfgang et al. teaches the question remains, "what are the downstream components"? Wolfgang et al. thus supports the position that additional, undue experimentation must be performed before the claimed invention can be made and used to treat cancer.

In conclusion, although carefully considered, Applicant's arguments and the merit of the declaratory evidence have not been found to overcome a preponderance of factual evidence of record that the supporting disclosure is not sufficient to meet the enablement provision of 35 U.S.C. § 112, first paragraph.

New Grounds of Objection

19. Claim 45 is objected to under 37 CFR 1.75 as being an exact duplicate of claim 2. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

20. Claim 58 is objected to as being drawn in the alternative to the subject matter of non-elected inventions. Appropriate correction is required.

21. Claim 58 is objected to because the conjunction "or" has been inadvertently omitted immediately following "(b) a substantially purified nucleic acid encoding the polypeptide of claim 4 in an expression vector;". Appropriate correction is required.

Conclusion

22. No claims are allowed.

23. Applicant's amendment necessitated the new ground(s) of objection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. This application contains claims 29-33, 36-44, and 48-55 drawn to an invention nonelected with traverse the paper filed November 11, 2004. A complete reply to the final

rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

25. The art made of record and not relied upon is considered pertinent to applicant's disclosure. Cheng et al. (*Endocrinology*. 2003; **144** (8): 3433-3440) and Maeda et al. (*J. Biol. Chem.* 2002 Jan 4; **279** (23): 24561-24568) teach characterization of the TARP promoter and the intracellular localization of TARP, respectively.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
February 14, 2005

LARRY R. HELMS, PH.D
PRIMARY EXAMINER